NIH Genes and Environment Initiativ
Exposure Biology Program

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NIEHS

U.S. Department of He
National Inst
National Institute of Env

HHS Secretary's Initiative Announced Feb 8, 2006

Genes and Environment Initiative (GEI):

Two research components:

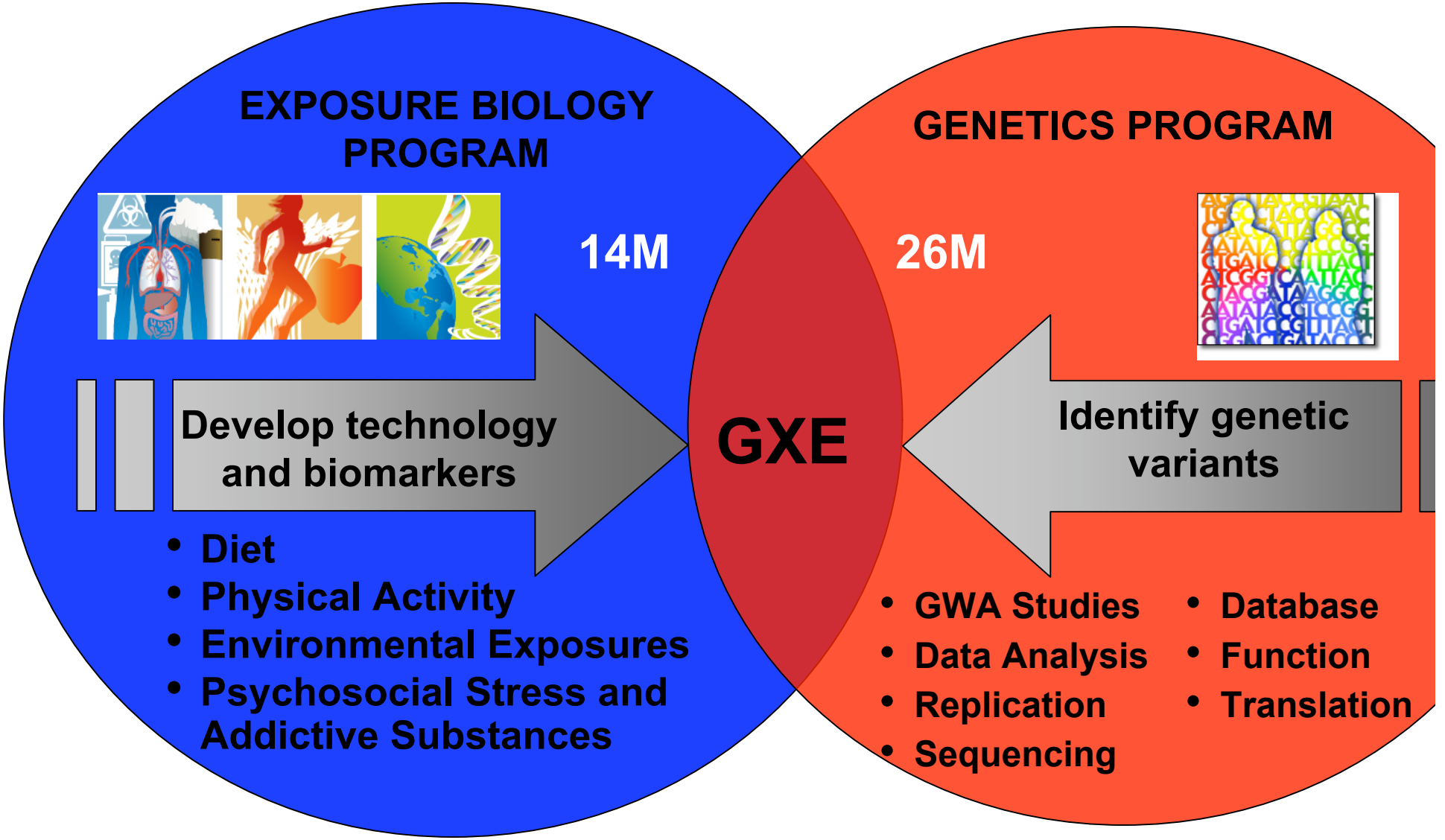
-- **Genetics Program**

-- **Exposure Biology Program**

NIH Coordinating Committee:

David Schwartz (NIEHS) and Francis Collins (NHGRI) to co-chair

Genes and Environment Initiative

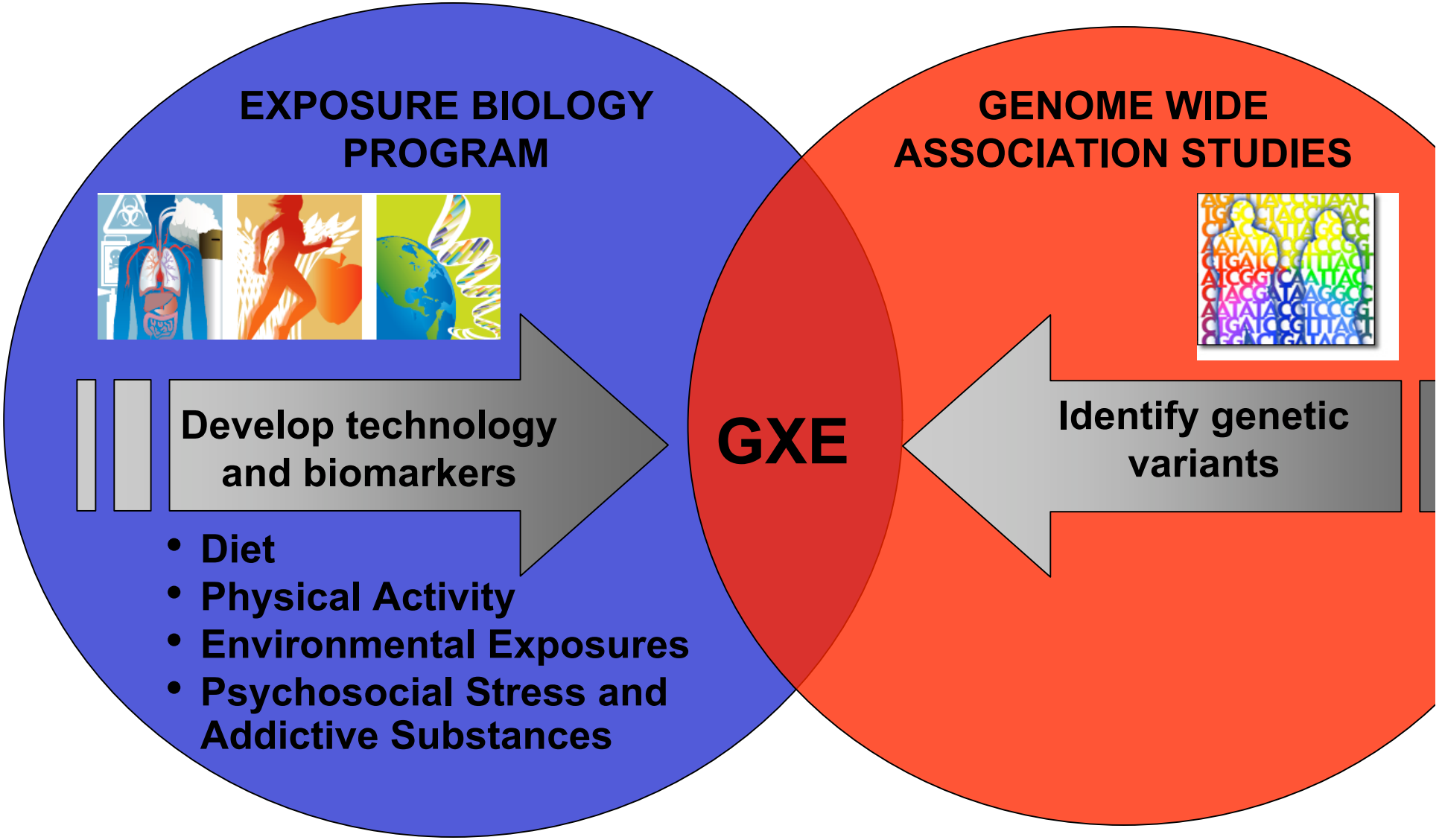


The Genes and Environment Initiative

Aims to accelerate understanding of genetic and environmental contributions to health and disease

- **NIEHS funding for projects starting in FY06: *Environmental Airway Project***
- **NIH-wide funding beginning FY07:**
  - **$26M/yr for genetics program, $14M/yr for exposure biology program**
  - **Managed by NIH-wide Coordinating Committee**

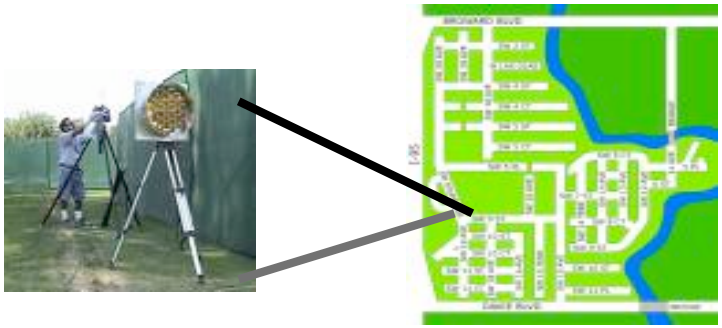
Genes and Environment Initiative: Exposure Biology Program



EXPOSURE SCIENCE TOOLS

CURRENT **FUTURE**

- **Ambient Monitoring**
  Large geographic scale, not specific to individuals



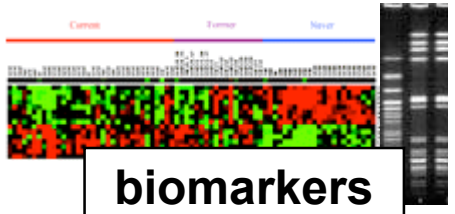
- Personalized
- Portable, deployabl
- Quantitative
- Real-time measurer

- **Biomonitoring**
  One time measurement, what does it mean?

Who is exposed?

How much?

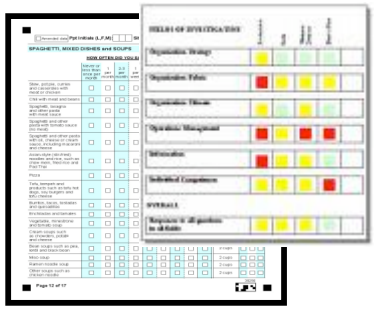
How often?



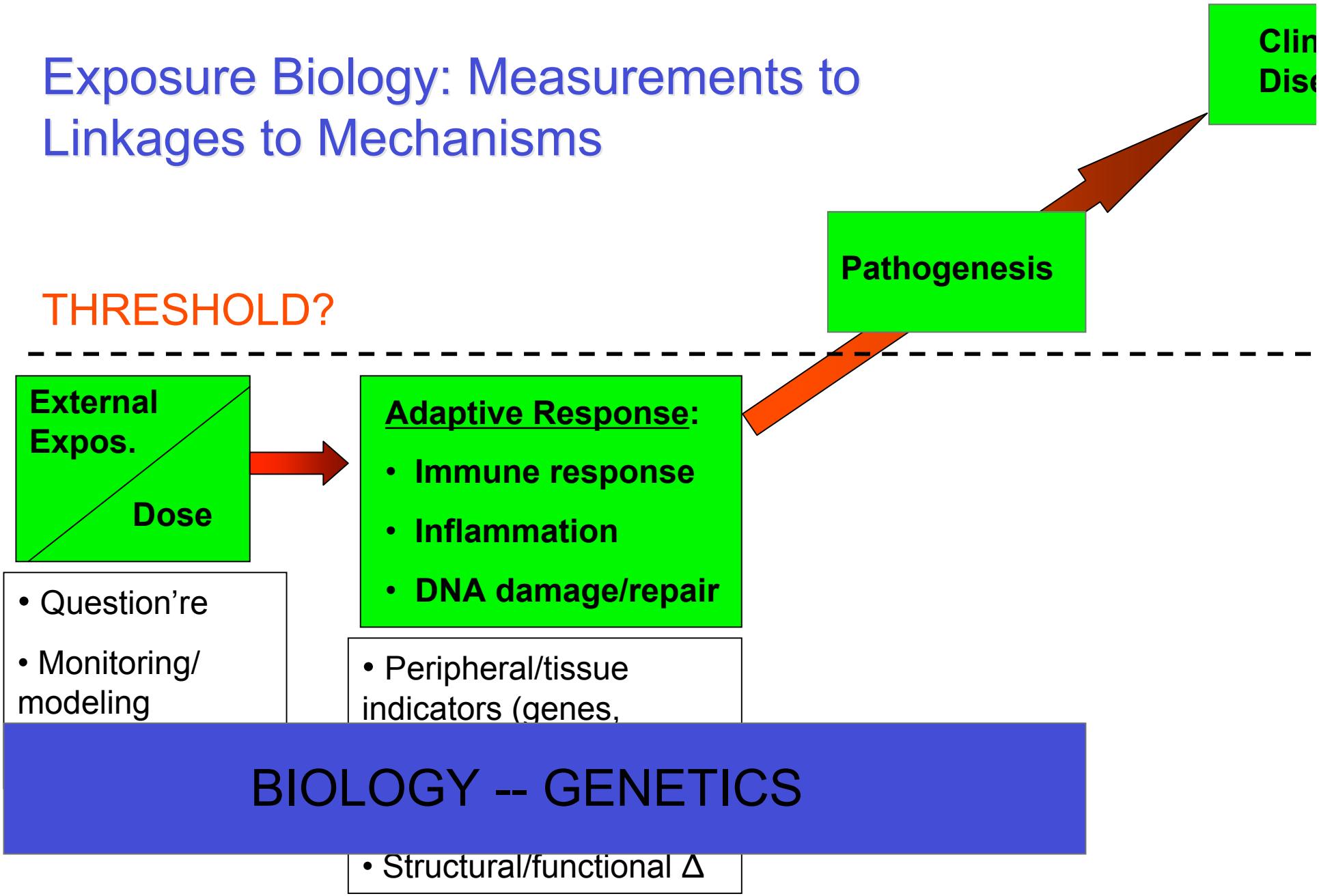
biomarkers

devices

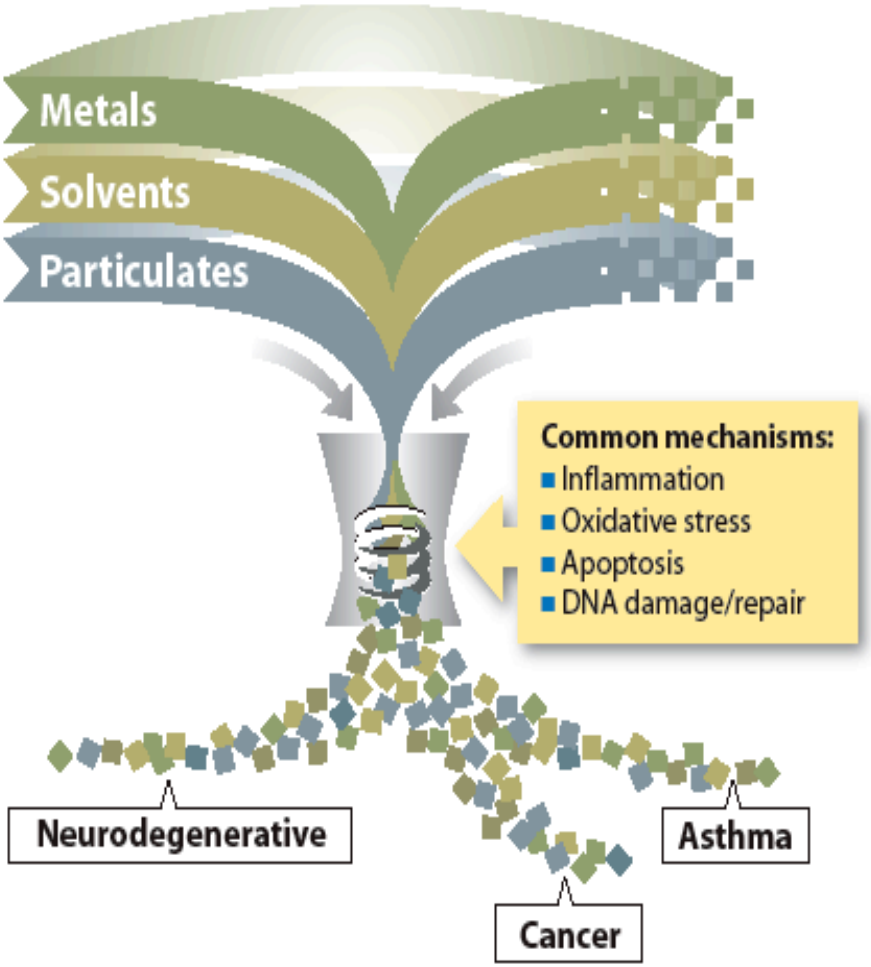
- **Questionnaire**
  One-time measurement, recall bias



Exposure Biology: Measurements to Linkages to Mechanisms

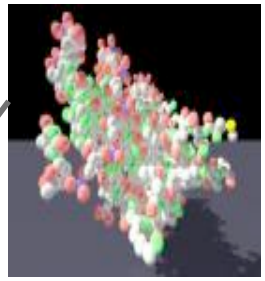


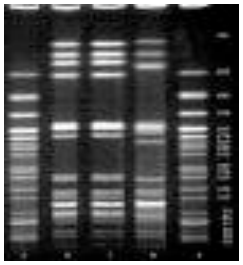
Exposure Biology Program: Focus on Common Mechanisms



Exposure Biology Program: match precision of exposure measurements and genetics

Personal genetic analysis (SNPs)

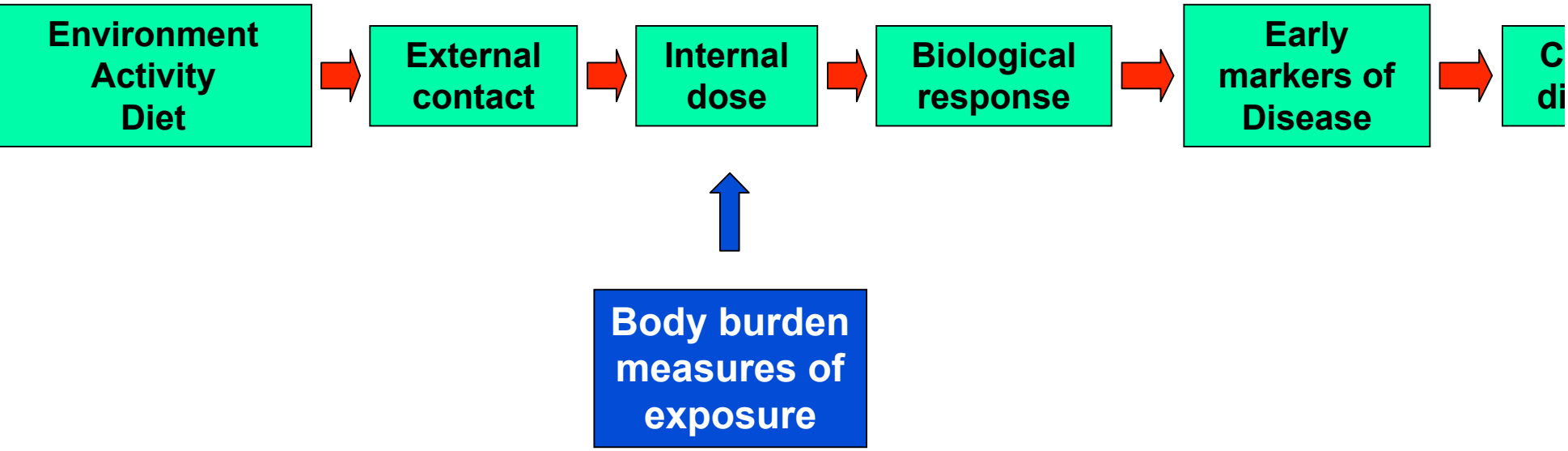




Personal exposure measurements

We need t
same leve
precision
genetic a
exposure
to study GX
disease

Exposure Assessment: Need More Precise Markers of Exposure

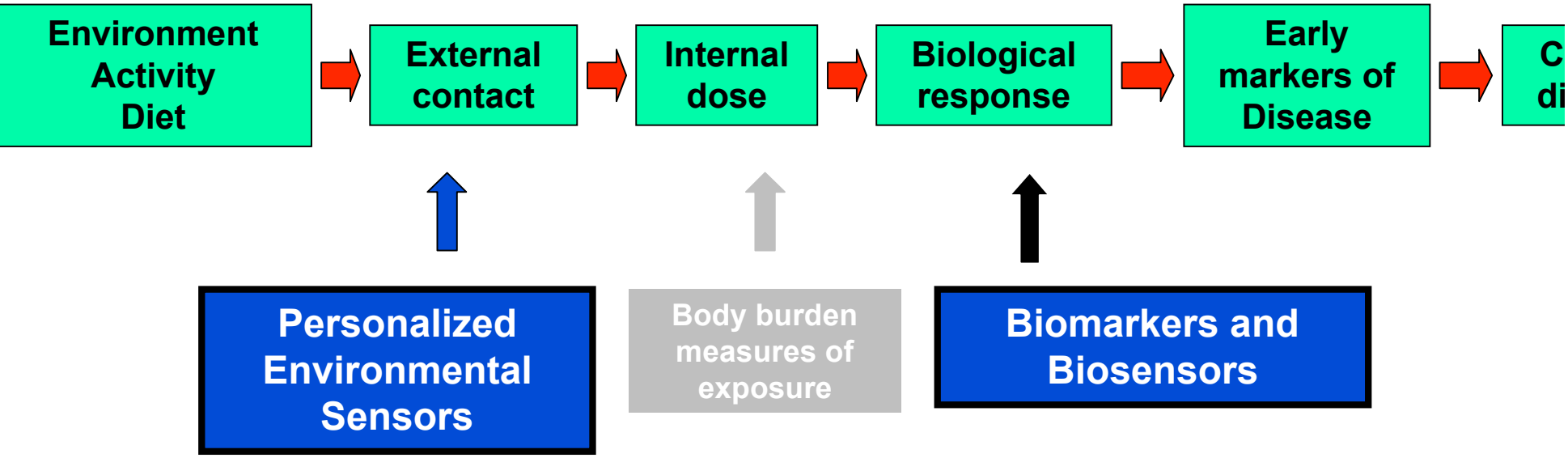


CDC: National Report on Human Exposure to Environmental Chemicals [148 Chemicals Measured]

- **Metals**
- **Tobacco (cotinine)**
- **PAHs**
- **Dioxins, Dibenzofurans**
- **PCBs**
- **Phthalates**
- **Phytoestrogens**
- **Organochlorine and Organophosphate pesticides**
- **Herbicides**
- **Other pesticides and insecticides**

http://www.cdc.gov/exposurer

Exposure Biology Program: Areas of Emphasis



Links personal exposures to biology to disease

Exposure Biology Program: Budget

	FY06	FY07	FY08	FY09	FY10	TOTAL
GEI		14,000	14,000	14,000	14,000	56,000
NIEHS	4,000	5,600	5,500	8,450	8,450	32,000
TOTAL		19,600	19,500	22,450	22,450	88,000

Environmental Airway Disease Project (FY06)

To further our understanding of genetic and environmental contributions to human airway diseas

Through….

- **Development of new assays and methods to more precisely measure exposure and genetic susceptibility to environmental stressors for airway disease**
- **Development of integrated panels of markers that reflect critical biologic processes in disease pathogenesis (innate immunity, oxidative damage)**

Rationale

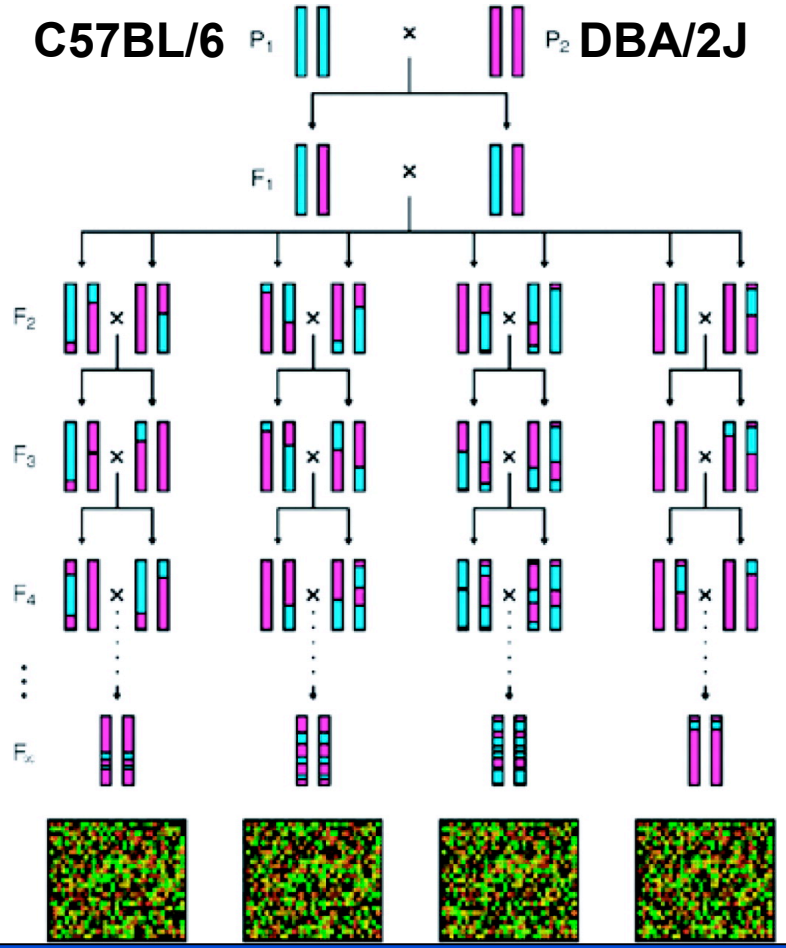
- Airway disease (asthma, COPD, and bronchitis) are major public health burdens
- Strength within NIEHS research portfolio
- Fundamental mechanisms of airway injury are known to involve innate immunity (inflammation, airways hyper-reactivity/hyperpermeability) and oxidative damage
- Genetic contribution to disease: strain differences in response
- Lack of precise, reliable, or consistent measures of exposur and response

Environmental Airway Disease Project

Study 1: **Genetic Susceptibility to LPS-Induced Airway Response in BXD Murine Strains**

Study 2: **Markers of Innate Immunity and Oxidative Damage in Response to Ozone, LPS, Cigarette Smoke and Cockroach Allergen in Genetically Divergent Murine Strains and Humans**

Study 1: Genetic Susceptibility to LPS-Induced Airway Respo in BXD Murine Strains



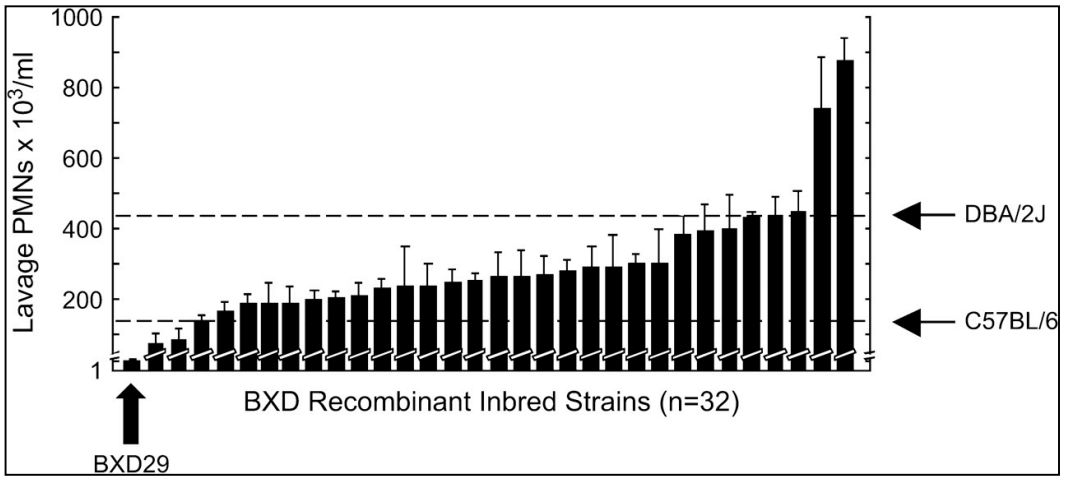
Construct RI strains by mating founder strains

Repeated sibling mating t produce many inbred lin that are genetically “fixe at each loci

Each strain represents a distinct genetic mosaic of the 2 parental strains

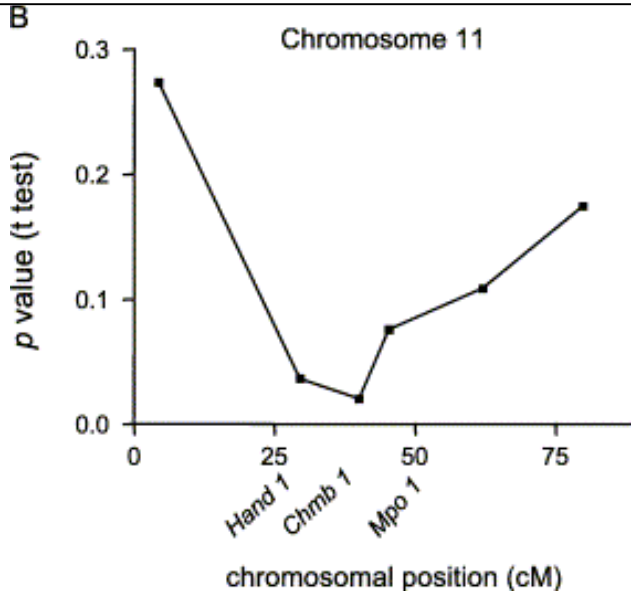
Use BXD Strains to Identify Genetic Susceptibility L for LPS Response

- Founder strains selected because both are WT for TLR4 and have differential response to LPS-induced inflammation
  - DBA/2J = high responder
  - C57BL/6 = low responder



Cook et al. *Genetics* 2006

Use differential sensiti to inflammation to m QTLs



QTL associated with LI induced inflammatio localized on chr11

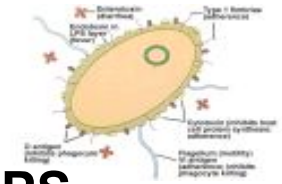
Next Steps

- Repeat with additional BXD RI strains (100 total
- Define phenotype by
  - Inflammation (Luminex assay)
  - Global methylation
- Identify QTLs and conduct fine mapping of putative loci using gene expression analysis (eQTLs) or other techniques

Study 2. Markers of Response to Ozone, LPS, Cigarette Smoke and Allergen

Exposures

- **Ozone**
- **Allergen**



- **LPS**

- **Cigarette smoke**

- 129S1/SvImJ
- A/J
- AKR/J
- BALB/cByJ
- BTBRT+tf/J
- C3H/HeJ
- C57BL/6J
- CAST/Ei
- DBA/2J
- FVB/NJ
- KK/HlJ
- Molf/EiJ
- NOD/LtJ
- NZW/LacJ
- PWD/PhJ
- WSB/EiJ

Innate Immunity

Oxidative Damage

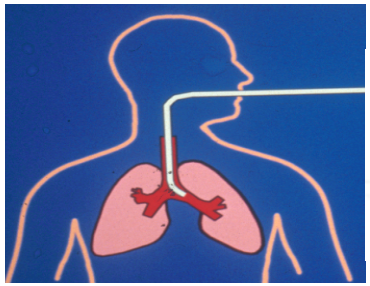
Molecular markers reflect changes in DNA/RNA adducts, proteins, metabolites

Tracking?

- Pulmonary function, airways reactivi
- Inflammatory cells, cytokines, chemokines, IgE
- Lung histology

Study Design

New murine samples:
10-16 strains
(NTP-Battelle)



Existing (archived) samples: m
human (challenge/epi)

Biosample Repository

(NIEHS/NTP - Battelle)

LIMS

Shared samples

Develop panels of biomarkers across model systems

Metabolomics

Epigenetics

Data Repository: shared access

Exposure Biology Program: Research Initiatives (FY07-10)

Environmental Sensors ($10M/yr, FY07-FY10)

- -Diet and physical activity ($4M/yr; NCI/NHLBI)
- -Chemical/biologic agents ($4M/yr; NIEHS)
- -Psychosocial stress and addictive substances ($2M/yr; NIDA)

Biologic Markers of Response ($4M/yr; FY07-FY10)

- -Pathogenic mechanisms that are common to various forms of environmental stress ($4M/yr; NIEHS)

Integrate Biomarkers and Biosensors ($4.5M/yr; FY07-FY10)

- -Centers that integrate biomarkers and field deployable biosenso ($4.5M/yr; NIEHS)

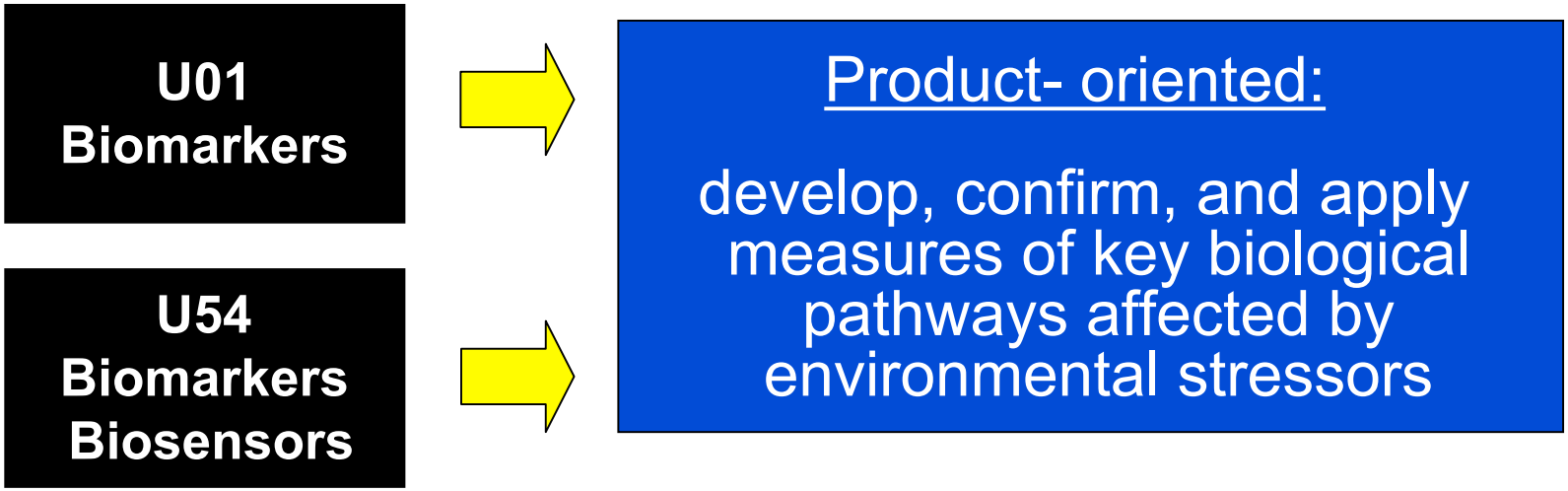
Application to GWA studies ($2.95M/yr; FY09-FY10)

Psychosocial Stressors Workshop (100K/FY07; OBSSR)

Opportunity Fund ($1M/yr; FY07-FY10)

RFAs released October 2006, funded in July 2007

RFAs on Biomarker Development



Goal: **products available for application to large-scale studies soon after the end of the four-year funding period.**

Biomarker (U01):

- An indicator of biologic response to an environmental exposure or stressor that is objectively measured
- Multiple markers will likely be needed to characterize the full response to the stressor
  - Molecular signatures defined by changes in gene expression, proteins or metabolites
  - Physiologic and biochemical parameters track with molecular changes

Biosensor (U54):

- Examples include lab-on-a-chip and microfluidics platforms molecular imaging technologies, and molecular probes

Research Topics of Interest for Biomarker RFAs

- Development of single or multiple biomarkers of response to environmental stressors
- Comparison of patterns of response across species, including humans
- Comparison of panels of biomarkers progressing from invasive to noninvasive specimens
- Acute vs. chronic exposure
- Study of biological responses under different exposure conditions – dose, frequency and timing of exposure

Components of GEI Exposure Biology Program and Estimated Proportion of Fundin

Component	Estimated Proportion (%)	IC Le
Environmental Sensors		
Diet and Physical Activity	18%	NCI/NH
Chemical and Biological Agents	18%	NIEH
Psychosocial Stress and Addictive Substances	9%	NIDA
Biomarkers of Response		
Biomarkers of Response	18%	NIEH
Centers – Biomarkers/Biosensors	20%	NIEH
Application to GWA Studies	7%	TBD
Opportunity Fund	5%	Sub-Comr

Exposure Biology Program: Deliverables

FY07	FY08	FY09	FY10	FY11

Environmental Sensors

- Diet/Physical Activity — U01 SBIR
- Chemicals/Biologics — U01 SBIR
- Psychosocial Stress/Addictive Substances — U01 SBIR

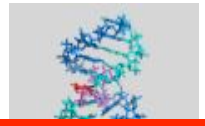
DEVICES

APPLICATION

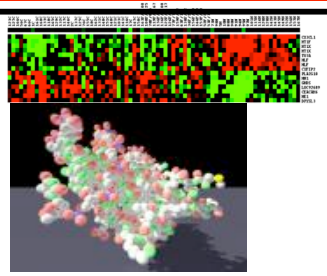
GW

Biological Response

- Biomarkers — U01
- Centers – biomarkers/biosensors — U01



FINGERPRINTS



U54 SBIR

DEVICES

Genes and Environment Initiative